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Systematic review

Boosting imaging defined dominant prostatic tumors: A systematic review

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ABSTRACT

Introduction: Dominant cancer foci within the prostate are associated with sites of local recurrence post radiotherapy. In this systematic review we sought to address the question: "what is the clinical evidence to support differential boosting to an imaging defined GTV volume within the prostate when delivered by external beam or brachytherapy".

Materials and methods: A systematic review was conducted to identify clinical series reporting the use of radiation boosts to imaging defined GTVs.

Results: Thirteen papers describing 11 unique patient series and 833 patients in total were identified. Methods and details of GTV definition and treatment varied substantially between series. GTV boosts were on average 8 Gy (range 3–35 Gy) for external beam, or 150% for brachytherapy (range 130–155%) and GTV volumes were small (<10 ml). Reported toxicity rates were low and may reflect the modest boost doses, small volumes and conservative DVH constraints employed in most studies. Variability in patient populations, study methodologies and outcomes reporting precluded conclusions regarding efficacy.

Conclusions: Despite a large cohort of patients treated differential boosts to imaging defined intra-prostatic targets, conclusions regarding optimal techniques and/or efficacy of this approach are elusive, and this approach cannot be considered standard of care. There is a need to build consensus and evidence. Ongoing prospective randomized trials are underway and will help to better define the role of differential prostate boosts based on imaging defined GTVs.

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Prostate cancer is a multi-focal disease and conventional therapies address this by treating the whole gland. In the case of radiation, such an approach however, may be limiting to the efficacy of radiotherapy as escalation of dose to improve tumor control may be limited by adjacent organ at risk tolerance [1].

Whole mount prostate pathology studies suggest in many cases a dominant cancer focus exists within the gland and may be a driver of the aggressiveness of the cancer and the epicenter of recurrence post treatment [2,3]. Thus strategies to identify and intensify treatment to dominant prostate foci (Gross Tumor Volume/GTV) are under active investigation. Advances in Positron Emission Tomography (PET), Single Positron Emission Tomography (SPECT) and magnetic resonance imaging (MRI) show promise in identifying prostate GTVs and advances in precision radiotherapy enable dose intensification [4–8]. In this systematic review we sought to address the question: "is there clinical evidence to support differential boosting to an imaging defined GTV boost within the prostate when delivered by external beam or brachytherapy (low dose or high dose rate)". In particular we were interested in techniques used for GTV definition on imaging for boosting and clinical endpoints of toxicity (both acute and late) and efficacy (biochemical and clinical control) among men so treated.

Materials and methods

Formulation of the research question, search strategy and data extraction elements were agreed upon by the lead authors (GB,CM) in advance of the literature review. A search of the PubMed database for the years January 1, 2000–June 30, 2012 was conducted using the following search strategy "(intraprostatic[tw] OR intraprostatic[tw] OR DIL[tw] OR ipl[tw]) AND (radiation[tw] OR radiotherapy[tw] OR brachytherapy[tw]) AND prostate[tw]". Papers describing focal salvage treatment (e.g. Nguyen [9] image guidance for whole gland therapy (e.g. Menard [10]) or partial gland therapy based on anatomically defined (not lesion defined) targets (e.g. Nguyen [11]) or where a focal boost was based exclusively on biopsy results (e.g. Gaudet [12]) rather than lesion imaging were excluded. Papers included needed to available as full published manuscripts, available in English and reporting at least one clinical

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outcome (toxicity or efficacy) among treated patients (papers reporting planning studies without actual patient treatment and single case reports were not included), Full text versions of the eligible papers were retrieved and reviewed including manual searching of the bibliographies for other applicable papers. In the case of one paper [13] the corresponding author was contacted for additional information regarding clinical outcomes and this lead to the identification of a companion paper [14] with this information. For the review, data extracted for each series included year of report, number of patients treated, proportion of low, intermediate and high risk patients (NCCN criteria) included in the series, median PSA among the patient population, methods used for GTV imaging and GTV delineation criteria, PTV1 delineation criteria, boost technique used and dose of the boost, use of supplementary pelvic nodal or androgen deprivation therapy, acute and late toxicity observed (along with toxicity scale used) clinical outcomes (clinical and/or biochemical control) and series specific observations were extracted. Nomenclature regarding intra-prostatic lesion definition differed significantly between patient series; for the purposes of this systematic review, GTV refers to imaging defined intra-prostatic lesions; PTV1 refers to the volumetric expansion on the GTV for the boost and PTV2 refers to the volumetric expansion of the whole prostate volume to account for setup and delivery uncertainty. Initial data extraction was undertaken by one author (GB) with review by a second author (CM). The remaining authors (MH, UVH) contributed to the analysis and interpretation of the extracted results and the manuscript. Given the heterogeneous nature of the patient series reported, no formal attempt at a quantitation of bias or analysis of pooled results was attempted however qualitative appraisal of the relative strengths and weaknesses of the individual series was made and qualitative statements are included in the results and discussion of the papers. The primary outcomes of interest were safety (toxicity reported), efficacy (clinical and biochemical control) as well as method of lesion delineation.

Results

In total, thirteen papers describing eleven unique patient series with a total of 833 patients were identified for data extraction. A flow diagram of the search results is available in Fig. 1. As outlined in Table 1, the analyzed literature [13–25] included patients treated with external beam (EBXRT) focal boost ($n = 5$ with simultaneous boost; $n = 1$ with sequential boost) as well as low dose rate brachytherapy (LDR, $n = 4$) and high dose rate brachytherapy (HDR, $n = 1$). Heterogeneity between the series restricted analyses to qualitative descriptions and pooling of results of data was not possible. The majority of series were prospective series examining relatively small numbers of patients. The largest external beam series (Fontenye et al. [24–26]) was limited by its retrospective nature and lack of an MRI panel confirming to current standards [4]. The largest brachytherapy series (Ellis et al. [27]) utilized an imaging modality with recognized technical challenges in interpretation and limited histopathologic validation. Approximately one quarter of the patients described met the NCCN criteria [28] for low risk. Androgen deprivation therapy varied among series as did the use of nodal radiation. Techniques for GTV definition used Standard Uptake Value (SUV) thresholds on ^{111}In-Capromab SPECT ($n = 2$) or ^{18}F-Fluorocholine PET imaging ($n = 1$). MRI based series (8) generally used a 1.5T magnet with endorectal (ERC) and pelvic coils. The T2W sequence was most commonly used (GTV = decreased intensity with a mass like appearance) with Dynamic Contrast Enhanced (DCE, GTV = increased enhancement); Diffusion Weighted derived apparent diffusion coefficient

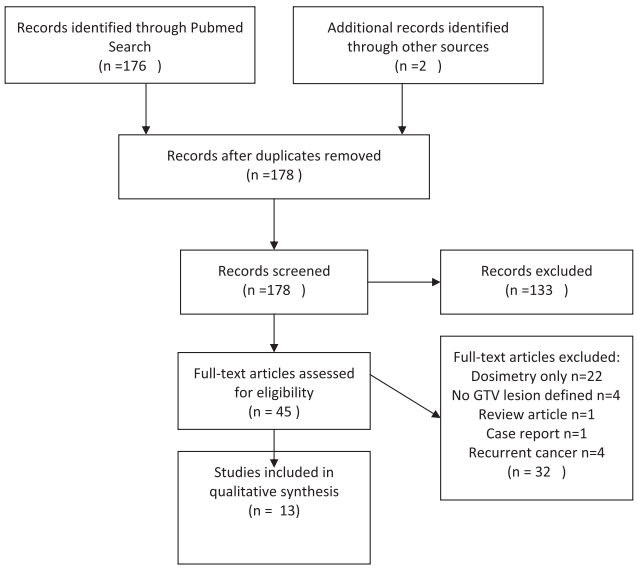

Fig. 1. PRISMA diagram of systematic review results.

maps (DWI/ADC, GTV = regions of decreased ADC values) or magnetic resonance spectroscopy (MRSI, GTV = increased choline + creatinine:citrate ratio) used less often. Only one series [25] utilized T2W + DWI + DCE which reflects the current consensus guidelines for prostate imaging [26,29]. Imaging defined GTVs were transferred to planning images (Computed Tomography/CT or Ultrasound/US) through image registration ($n = 6$) or manual transfer/"cognitive fusion" ($n = 5$). Where reported, GTV volumes ranged from 3.5–6.8 ml; multiple GTVs were defined in 10% of patients and close GTV proximity (<3–5 mm) to Organs at Risk (OAR) was noted. Most series defined a PTV1 (most commonly 3–4 mm, excluding OAR) for the GTV. For EBXRT series, PTV2 doses ranged from 64–78 Gy; PTV1 doses from 80–94.5 Gy. The average differential dose (PTV2–PTV1) was 8 Gy (BED2, $a/b = 3$ Gy, range 3–35 Gy). The most common EBXRT rectal dose constraints was V70 <15–30% with rectal Dmax of 76–80 Gy; bladder constraints were V70 <15–30% and Dmax of 80 Gy. For the brachytherapy series, ^{125}I LDR was most commonly used with a PTV2 dose of 145 Gy, a PTV1 dose of 217 Gy (150%) and Dmax to urethra of <130–150%. Median follow-up ranged from 3–66 months. Outcomes reported included biochemical control in 4 series and toxicity in 10. Grade 4 toxicity was reported in 4 patients (3 rectovesical fistula, 1 hematuria) [17,20,23]. The series with the highest boost differentials [22,23] included 66 patients with reported late Grade 3 or greater toxicities that ranged from 0 to 10% including one patient with fistula formation.

Discussion

Histopathologic studies and patterns of recurrence after external beam radiotherapy suggest that many men may have a dominant focus of disease in the prostate that is a key driver of cancer biology and treatment success [2,30]. Evolution of prostate cancer imaging [4–6] and radiation treatment [7] has driven the exploration of focal intra-prostatic dose escalation. Consensus statements and prospective trials regarding the implementation of therapies based on the identification of focal intra-prostatic lesions are emerging [31–33]. Concerns regarding therapies addressing the focal lesion only are the difficulty in identifying men with truly focal disease [2] and the high risk of recurrence noted to date when less than whole gland treatment is attempted based on

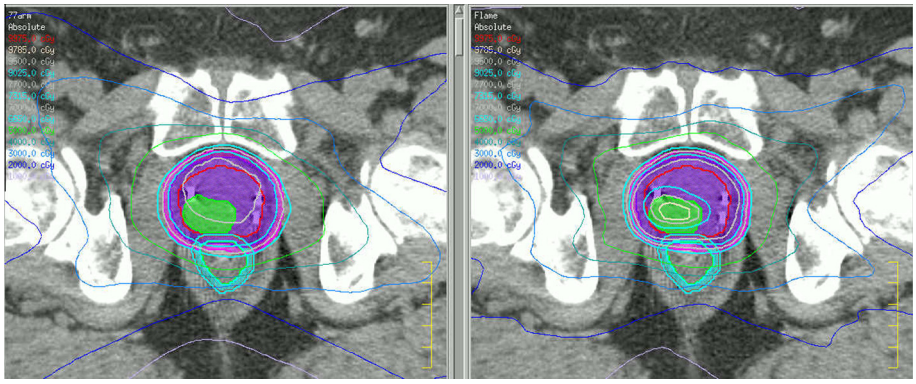

Fig. 2. An example of the dose distribution of a patient enrolled on the FLAME randomized controlled trial. Left- A standard dose of 77 Gy in 35 fractions is delivered to the prostate and seminal vesicles. Right- An illustration of an integrated boost of 95 Gy delivered to the GTV with compromised posterior coverage adjacent to the rectum.

strategies without explicit lesion targeting [11,34]. For this reason, differential boosting of the prostate with dose escalation to imaging defined intra-prostatic GTV volumes is attractive. In this systematic review, a variety of approaches attempting to exploit this strategy were identified. The variability in approaches reflects the lack of consensus around key issues that need to be addressed in order to rigorously assess the efficacy and safety of this approach.

Optimal intra-prostatic GTV boost dose

There have been numerous studies modeling the benefit and safety of incorporating a boost of dominant intra-prostatic GTV(s) with whole prostate treatment (see Supplementary References) and an example is illustrated in Fig. 2. The majority of studies modeling GTV boosts used MRI for GTV delineation with fewer using PET or SPECT. Anatomy dependence is noted with boosts more achievable if GTVs are located more than 3 mm from OAR. Like the clinical data reported here, modeling studies suffer from lack of consistent methodology for GTV delineation and deformable mapping onto planning images. The series by Huisman and Van Lin are notable in that they describe planning workflow in detail and use intra-prostatic fiducial markers to assist in image fusion as well as image guidance for treatment [35,36]. In general, planning studies suggest that GTV dose escalation up to 95 Gy with external beam radiotherapy should be feasible for most patients with a resulting absolute increase in TCP of 2–15%. The ideal GTV dose remains to be determined however and higher doses that respect OAR tolerances may be difficult to achieve for all patients depending on the anatomic location of the dominant lesion and plateaus in TCP beyond doses of 84–90 Gy have been suggested [37,38]. Achieving a high boost dose at the expense of a lower (<70–75 Gy) whole prostate dose may be a counter-productive strategy as increased intraprostatic recurrences have been noted with this approach [11,34,49]. For example, D'Amico reported on a series of patients where MRI was used to define the peripheral zone as an "anatomic" GTV for dose escalated partial prostate brachytherapy and noted relatively high failure rates compared to whole gland brachytherapy series [11]. Clinically, both Schick and Miralbell [22,23] described series using relatively low (60 Gy) whole gland treatment with external beam radiotherapy followed by an intra-prostatic boost with HDR or stereotactic external beam boost. In both cases, boost volumes were generous and encompassed the majority of the gland (typically a horseshoe shaped boost with urethral sparing) which may have contributed to the relatively favorable control rates seen (78% and 98% 5 year bDFS respectively).

Standards for GTV delineation

The potential benefits of intra-prostatic boosts are dependent on the performance of the imaging techniques used for GTV delineation [40]. Within the series reviewed imaging used for GTV definition including single parameter MRI, multi-parametric MRI, SPECT and PET imaging. Of these imaging modalities, MRI has the strongest evidence base validating MRI against pathology gold standards (see Supplementary References) but even then considerable variability in methodology between these reports exist. Most MRI validation studies used 1.5T with pelvic and ERCs and evaluated mainly intermediate and high risk patients. T2W was routinely used with variable incorporation of other sequences (DCE, DWI, and MRSI). Criteria for lesion identification differed considerably between series with some series using qualitative "suspicion scales" to score sectors or regions "benign" to "definitely malignant" based on combinations of imaging traits to more quantitative measures based on perfusion or spectroscopy parameters. In general, test performance (as measured by sensitivity/specificity or ROC analysis) is worst for single sequence MRI (performance around 0.6–0.7) with performance improving for multi-parametric MRI (performance 0.8–0.9) and this is reflected in current consensus guidelines recommending T2W + DWI + DCE for lesion detection [26,29]. As an example, Futterer [41] reported on 34 patients, intermediate risk, imaged with 1.5T, T2W, DCE and MRSI and noted that a multi-parametric score of MPKS (mean score of DCE parameters) + spectroscopy provided the best performance (ROC Az = 0.94). There is less information regarding performance of MRI in defining boundaries of lesions compared with pathology (as opposed to identifying the presence of cancer on a quadrant or sextant basis). Variations in malignant gland density and sparse tumor distribution can affect visibility of prostate cancer with MRI and confound lesion delineation [42]. Where reported, modest concordance levels lesion boundaries on imaging and pathology are noted (0.6–0.7) with expansions of imaging boundaries by 2–5 mm to account for imaging and registration uncertainties improving concordance indices [43–46]. Probability maps generated by statistical models have demonstrated excellent concordance with pathology defined GTVs in the peripheral zone [44,47,48] and could be incorporated into radiation "dose painting" treatment planning [49] but still require validation in larger patient cohorts and across institutions. Finally, biopsy confirmation of suspicious targets identified on imaging may be considered in order to exclude a subset of patients with false-positive imaging findings [25]. Such image guided biopsies may address the uncertainty associated with the planning of boost therapies based on random systematic biopsies of the prostate alone [12] by allowing precision localization of involved biopsies while avoiding the cost

Table 1
Literature summary.

Reference	Patient population	Tumor volume delineation	Treatment	Outcomes
Ippolito Ref. [19]	*N* = 40 Median PSA: 7 LR: 4 IR: 17 HR: 19	1.5 TMRI + ERC; sequences not specified; fusion; GTV 'defined on MRI, consistent with biopsy findings' PTV2 = prostate + SV + 1 cm PTV1 = GTV + 5 mm	5 field IMRT; 6MV PTV2: 72 Gy PTV1: 80 Gy (84 Gy *a*/*b* = 3)	Survival No biochemical failures GI toxicity (RTOG/EORTC) Acute: 15% Grade 2; 5% Grade 3 Late: 5% Grade 2; 2.5% Grade 3
Prospective feasibility study; IRB approved	Median follow-up 19 months	Median PTV1 volume 55 ml	Additional treatments 100% ADT	GU toxicity (RTOG/EORTC) Acute: 30% Grade 2; 2.5% Grade 3 Late: 5% Grade 2; 2.5% (1/40) Grade 4 2 year actuarial risk of toxicity >Grade 2 was 13% (GU); 9.5% (GI)
Pinkawa Ref. [13,14]	*N* = 66 Median PSA: 14 LR: 23 IR: 21 HR: 22	18F-Fluorocholine PET; fusion; GTV SUV >2 times background	5 field, 15 MV IMRT	Survival NR
Prospective quality of life study; IRB not specified	Median follow-up 19 months	PTV2 = prostate + SV + 4–8 mm PTV1 = GTV + 3–4 mm	PTV2 = 76 Gy PTV1 = 80 Gy (83 Gy a/b = 3)	GI/GU Toxicity (EPIC) 10% deterioration in brother and function scores at median of 2 months post radiation; return to baseline by median of 19 months. No difference between patients who received an SIB (*n* = 46) vs. no SIB(*n* = 21)
	Extra-prostatic disease was detected in 1/66	mean GTV 6.2 ml; 22 had 2 GTV; 7 had 3 GTV defined; 36 GTV had involvement of central gland; 36 GTV were within 3 mm of rectum;	Additional treatments 16% ADT	
Wong Ref. [20] Prospective feasibility study, IRB approved	*N* = 71 Median PSA: 6.1 LR: 28 IR: 40 HR: 3	111In-Capromab SPECT; fusion; GTV = SUV 3× muscle SUV	5 field IMRT; 6MV	Survival 94% 5 year BDFS; 93% 5 year OS (Phoenix)
	Median follow-up 66 months	PTV2 = prostate + SV + 6 mm PTV1 = GTV Median GTV = 7% of PTV2	PTV2: 75.6 Gy PTV1: 82 Gy (85 Gy *a*/*b* = 3) Additional treatments 60% ADT	GI Toxicity (Modified RTOG) Acute: 45% Grade 2 Late: 15% Grade 2 GU Toxicity (Modified RTOG) Acute: 54% Grade 2; 1% Grade 3 Late: 39% Grade 2; 3% Grade 3; 1% Grade 4
Ellis Ref. [17,18,27]	*N* = 239 Median PSA: 7.6 LR: 116 IR: 72 HR: 51	111In-Capromab SPECT gamma contrast uptake "dialed in" to correlate with biopsy. No fusion	LDR prostate brachytherapy	Survival 85% 10 year BDFS; 85% OS (Phoenix)
Prospective study, IRB approved	111In-Capromab SPECT suggested metastatic disease in 9.2% Median follow-up NR	PTV2 = prostate + 2–5 mm PTV1 = GTV + 5 mm	PTV2 = 108–144 Gy (I125) = 100–125 Gy (P103) PTV1 = 150% of PTV2 Additional treatments 37%: EBXRT 21%: ADT 27%: Node dissection	GI Toxicity (RTOG) Acute: 4% Grade 2; 0% Grade 3 Late: 2% Grade 2; 1% Grade 4 GU Toxicity NR Survival was worse for patients with extra-prostatic disease on SPECT. 2 patients had Grade 4 toxicity (fistula) at 18 and 30 months
Schick Ref. [23]	*N* = 77 Median PSA: NR LR: 7 IR: 9 HR: 61	A hemi-prostate (*n* = 20) or bilateral (*n* = 57) prostate GTV was defined by correlation of DRE, biopsy results and ERC MRI; if T2W changes and biopsy involvement confined to same lobe, unilateral boost otherwise bilateral boost; catheter + 3–5 mm used to define urethra PRV; no fusion	HDR prostate brachytherapy PTV2 = 64.4 Gy PTV1 = 88–104 Gy (*a*/*b* = 3)	Survival 78% 5 yr BDFS (Phoenix)
Prospective study; IRB not specified	Median follow-up 62–67 months	PTV2 = Prostate + SV PTV1 = GTV	Patients treated with an HDR boost after completing prostate EBXRT *N* = 19: 2 × 6 Gy	GI Toxicity (RTOG/EORTC) Acute: 3% Grade 2; 0% Grade 3/4 Late: 9% Grade 2; 4% Grade ¾ GU Toxicity (RTOG/EORTC)

(*continued on next page*)

Table 1 (*continued*)

Reference	Patient population	Tumor volume delineation	Treatment	Outcomes
			N = 21: 2 × 7 Gy *N* = 37: 2 × 8 Gy Additional treatments 81% ADT 36% PLN	Acute: 3% Grade 2; 3% Grade3/4 Late: 10% Grade 2; 9% Grade 3/4 Higher acute and late GU toxicity was noted for bilateral vs. unilateral boost; one patient (unilateral 2 × 8 Gy) developed a fistula requiring pelvic exenteration
Miralbell Ref. [22]	*N* = 50 Median PSA: NR LR: 5 IR: 12 HR: 33	GTV defined on ERC MRI (T2 + DCE) correlated with biopsy; fusion (ERC used for planning CT to facilitate); bilateral gland in 48;	3DCRT (*n* = 39) or IMRT (*n* = 11) PTV2 = 64 Gy PTV1 = 80–99 Gy (*a*/*b* = 3)	Survival 98% 5 year BDFS (Phoenix) GI Toxicity(RTOG/EORTC) Acute: 8% Grade 2; 0% Grade 3 Late: 10% Grade 2; 10% Grade 3
Prospective study; IRB not specified		PTV2 = prostate + SV+? PTV1 = GTV + 3 mm	stereotactic boost after completing prostate EBXRT*N* = 5: 2 × 5 Gy *N* = 8: 2 × 6 Gy *N* = 8: 2 × 7 Gy *N* = 29: 2 × 8 Gy Additional treatments 56% PLN 66% ADT	GU Toxicity(RTOG/EORTC) Acute:46% Grade 2; 4% Grade 3 Late: 12% Grade 2; 0% Grade 3 No statistically significant toxicity difference between high dose arm (8 Gy × 2) vs. lower dose arms; actuarial risk of >Grade 2 toxicity was 18% GU; 28% GI
Fonteyne Ref. [24]	*N* = 230 Median PSA: 11.2 LR: 17 IR: 97 HR: 116	GTV defined on 1.5T ERC MRI T2W or MRSI by consensus; 118/230 had MRI defined GTV; 4/118 were defined on MRSI; 8/118 had more than one GTV defined. Fusion	3–6 field IMRT; daily U/S guidance	Survival NR
Retrospective review; IRB not specified		PTV2 = prostate+/− SV + 4 mm PTV1 = GTV + 8 mm	PTV2: 78 Gy PTV1: 80 Gy (81 Gy *a*/*b* = 3)	GI Toxicity (modified RTOG) Acute: 11% Grade 2; 0% Grade 3 Late: NR GU Toxicity (modified RTOG) Acute: 41% Grade 2; 7% Grade 3 Late: NR 50% had boost to GTV; no difference in toxicity boost vs. no boost
Singh Ref. [25]	*N* = 3	GTV defined on 3T ERC MRI by T2W + DCE + DWI with biopsy confirmation; gold seed fiducials were used for fusion. 1 patient had 2 GTV	IMRT with daily image guidance	Survival NR
Prospective, phase I, IRB approved	Follow-up of 3–18 months	PTV2 = prostate + 7 mm PTV1 = GTV + 3 mm	PTV2 = 75.6 Gy PTV1 = 94.5 Gy	GI Toxicity (RTOG) Acute: 0/3 Grade >2 Late: NR GU Toxicity (RTOG) Acute: 2/3 Grade 2 Late: NR First cohort of a Phase I study that seeks to dose escalate the GTV to 152 Gy
DeMeerleer Ref. [15]	*N* = 38 Median PSA: 10.2	Three physician consensus read of 1.5T ERC MRI; GTV delineated on T2W (15/38 patients imaged had GTV defined); median volume was 4 cc; 13/15 were <5 mm from rectal wall; no fusion	3 Field IMRT	Survival NR
Retrospective review, IRB not specified	LR: 3 IR: 8 HR: 5	PTV2 = prostate + 7–10 mm PTV1 = GTV + 0 mm	PTV2 = 78 Gy PTV1 = 80 Gy	GI Toxicity Acute: 20% Grade 2; 0% Grade 3 Late: NR GU Toxicity Acute: 40% Grade 2; 7% Grade 3 Late: NR
Dibase Ref. [16] Prospective feasibility, IRB approved	*N* = 15 Median PSA: 7.1	1.5T ERC MRI spectroscopy used to manually map voxels with citrate: choline + creatinine ratio <1.4 onto axial US	LDR prostate brachytherapy	Survival NR
	LR: 15/15	PTV2 = prostate + 0–2 mm PTV1 = GTV	PTV2 = 145 Gy (I125) PTV1 = 188 Gy	GI Toxicity Acute: “No rectal morbidity”

Table 1 (*continued*)

Reference	Patient population	Tumor volume delineation	Treatment	Outcomes
	Median follow-up NR 1/14 not implanted			Late: NR GU Toxicity (modified RTOG) Acute: 53% Grade 2 Late: NR
Zelefsky Ref. [21] Prospective feasibility; IRB not specified	*N* = 4 Median PSA: 4.5 LR: 2 IR: 2	1.5T ERC MRI spectroscopy to identify voxels with high choline + creatinine: choline ratio; mapped to ultrasound as GTV using deformable registration PTV2 = prostate PTV1 = GTV	LDR prostate brachytherapy PTV2 = 100–145 Gy (I125) PTV1 = 150% of PTV2	Survival NR GI Toxicity NR GU Toxicity (modified RTOG) NR

LR, low risk; IR, intermediate risk; HR, high risk; ERC, endorectal coil; MRSI, magnetic spectroscopy imaging; BDFS, biochemical disease free survival; NR, not reported; ADT, androgen deprivation therapy; PLN, pelvic lymph node radiation.

and potential morbidity of intensive biopsy correlations through template or saturation biopsies either alone or with imaging as implemented by some investigators for GTV identification [32].

There are fewer studies of histopathologic validation of SPECT and PET. (see Supplemental References) In our review, two large series with long term follow-up reviewed defined GTVs using ^{111}In Capromab SPECT imaging. Ellis demonstrated a PPV/NPV of 0.68/0.88 using ^{111}In Capromab correlated with biopsy positive sectors among 7 patients [50]. Mouraviev [51], however, noted no correlation between ^{111}In Capromab uptake and the presence of cancer on whole mount pathology in 25 patients. Thus, continued use of ^{111}In Capromab for GTV delineation would seem ill advised unless there is further work to validating this imaging against histopathology. Kwee [52] compared ^{18}F-Fluorocholine PET imaging with whole mount pathology on a sextant basis. They found SUVmax correlated with sextant involvement and identified involved sextants with an overall accuracy of 0.72. When comparing ^{11}C-Choline to MRI among 23 patients Vandenbergh [53] noted ^{11}C-Choline had similar performance to T2W with an overall accuracy of 0.6–0.7 but PET approached MRI accuracy only for lesions >0.9 cm^3. Like MRI, automated thresholding techniques based on relative SUV may improve concordance with pathology and can be exploited for "dose painting" [39,54,55] however the limited histopathology correlative studies suggest caution in using PET as the sole modality for GTV definition.

Patient selection and outcomes reporting

In our review of the literature we were able to identify eleven unique patient series (833 patients) ranging from small preliminary experiences of 3–4 patients to large institutional series of over 200 patients. The EBXRT series reported were comprised of primarily intermediate to high risk patients; the brachytherapy series included a higher proportion of low risk patients. Among all series there was variability in patient populations, use of androgen deprivation (which may affect GTV definition [56]) use of nodal irradiation, length of follow-up and outcomes reporting that preclude definitive statements regarding efficacy of the boost techniques reported to date. While reported toxicity was generally noted to be low, many (56%) EBXRT patients had a very modest differential boost of 3 Gy and many of the brachytherapy patients had boosts which redirected expected "hot spots" into GTV regions. Furthermore, PTV1 coverage was sometimes compromised in order to respect conservative rectal dose constraints. Thus the toxicity profile noted in this review may not accurately reflect risks associated with more significant differential boosts (>10 Gy). It is perhaps somewhat reassuring that the series with highest boost ranges did not report dramatically different toxicity than the other series [22,23]. However, these series used relatively low whole prostate doses of 64 Gy and generous (hemi prostate or bilateral prostate GTV) volumes with relatively high HDR or stereotactic dose of 5–8 Gy × 2; complicating extrapolation to other treatment situations. Efficacy data are limited to reports of biochemical control at early (5 year) endpoints. No series reported on histopathologic outcomes (i.e. post treatment biopsies) as an early endpoint and this may be an opportunity for future clinical trials.

Recommendations

Despite a large cohort of patients treated with the use of imaging for delineating and delivering a GTV boost in prostate cancer conclusions regarding optimal techniques and/or efficacy of this approach are elusive, and the use of intra-prostatic GTV boost cannot be considered standard of care. The fact that dominant intraprostatic foci appear to be important drivers of cancer outcomes

justifies continued exploration of strategies for differential dose escalation however significant issues need to be addressed in order to rigorously evaluate the validity of this approach. Key issues identified through our review include the need for standardized, reproducible and accurate intra-prostatic GTV definition guidelines based on standardized imaging protocols using clinically validated tools for deformable registration of GTVs onto planning scans. In this regard PET/CT and SPECT/CT techniques carry the advantage of potentially simplified integration into clinical radiation planning workflow but the absence of rigorous histopathology validation of these modalities argues against these techniques. Multi-parametric T2W + DCE + DWI has the strongest histopathologic validation however the fusion of these images with planning CT scans for GTV definition is technically more challenging and subject to error especially when endorectal coil is used for imaging due to gland deformation. Robust motion management strategies to decrease the chance of geographic miss of the GTV are required. In this regard use of fiducial markers may be a preferred strategy as they may assist in the image fusion process and also facilitate daily image guidance. Appropriate clinical trial design for evaluating a strategy of GTV boosting need to be identified including stratification or otherwise controlling for variability in other treatment elements such as the use of pelvic nodal irradiation, hormone therapy use and patient selection (low vs. intermediate vs. high risk). Clinical trial endpoints of early and late toxicity are clearly needed with reporting by standardized toxicity scales (CTCAE or RTOG/LENT). Traditional clinical endpoints of biochemical control and disease free survival pose challenges for the efficient evaluation of new technologies in this disease. Prostate biopsies pre- and at 1–3 years post-treatment directed at both the "uninvolved" prostate as well as the imaging defined GTVs may be an appropriate surrogate endpoint and have been proposed as primary endpoints for trials of focal therapy [31]. Such biopsies could help validate GTV definition as well as characterize response in both the boosted and unboosted areas of the prostate although the use of biopsies as an endpoint needs to consider issues of timing and the challenge of interpreting histologic response post radiation [57] which may be more problematic compared to physical ablative therapies such as high intensity focused ultrasound, cryotherapy or focal laser ablation which produce well defined tissue effects [58]. Other proposed endpoints to be considered include toxicity and clinical efficacy. For example, a recent trial of focal therapy based on imaging and template biopsy targeting used erectile function as a primary endpoint with disease control and biopsy control [32]. Another unresolved issue in designing trials is the best technology for GTV boosting. At this time, both brachytherapy and external beam boosting strategies appear worthy of investigation. Both LDR and HDR are inherently inhomogenous in their dose distribution and "strategic placement" of expected hotspots (150%) in the imaging defined GTV regions should be feasible and reduces the potential for inter and intra fraction variation in delivery when external beam techniques are used for GTV boosting. Fusion of pre-treatment imaging with the ultrasound imaging used for brachytherapy remains a challenge however commercial solutions for MRI-ultrasound fusion for needle guidance are becoming available [59]. For external beam, there are many technologies available that can deliver differential boosting and the availability of in-room image guidance can potentially reduce errors due to inter or intra fraction motion [60]. An optimal GTV boost dose and fractionation has yet to be determined for external beam and several lines of investigation are underway. Current multi-institutional trials of GTV boosts based on multi-parametric MRI are underway including FLAME [61] and HEIGHT (clinicialtrials.gov NCT0141132) are evaluating a GTV boosts equivalent to 95 Gy with whole prostate doses in the range of 76–77 Gy. A phase II trial (clinicialtrials.gov NCT01409473) is examining a hypofractionated strategy with whole prostate doses in the range of 40–45 Gy/5 fractions with simultaneous boost of the GTV of 50 Gy/5. DELINEATE is a Phase II study examining the toxicity and feasibility of a dose escalated boost to magnetic resonance imaging identified tumor nodule(s) in localized prostate cancer [http://www.controlled-trials.com/ISRCTN04483921].

Conclusions

Available literature describes patients treated with modest boosts to intra-prostatic GTVs although standards for imaging, GTV delineation, treatment planning and dose remain to be determined and the available clinical series do not permit conclusions regarding the safety or efficacy of this approach. At the current time, this approach cannot be considered standard of care. Ongoing prospective trials are underway and will help to better define the role of differential prostate boosts based on imaging defined GTVs.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.radonc.2013.04.027.

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